Research Article

One-pot synthesis of pyrano[2,3-c]pyrazoles by using aqueous NaPTS as reusable catalyst at ambient condition

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Abstract

We have developed an efficient, simple and environmentally benign protocol for the synthesis of pyrano[2,3-c]pyrazoles in aqueous NaPTS hydrotropic solution at room temperature. The present method is bestowed with merits such as mild reaction conditions, short reaction time, easy work-up, high yields and green aspects through the avoidance of organic solvents and toxic catalysts. The aqueous hydrotropic solution presents good recyclability over five catalytic cycles.

Keywords: Multicomponent reactions, aq. NaPTS, pyrano[2,3-c]pyrazoles

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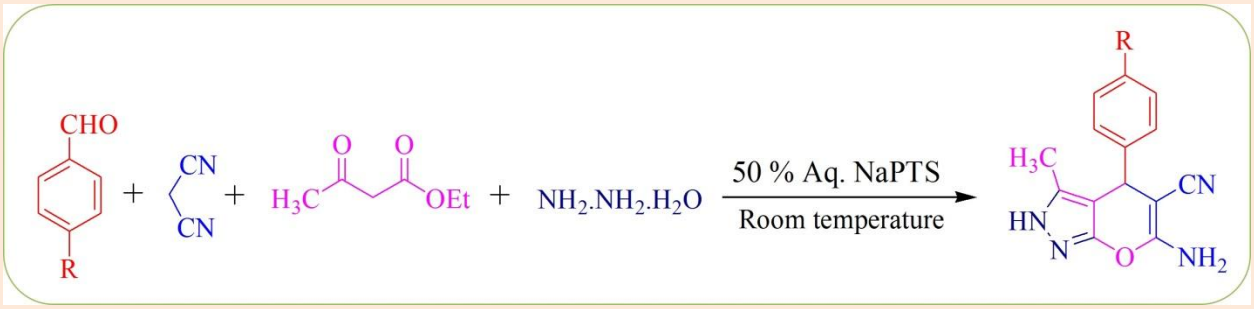


Introduction

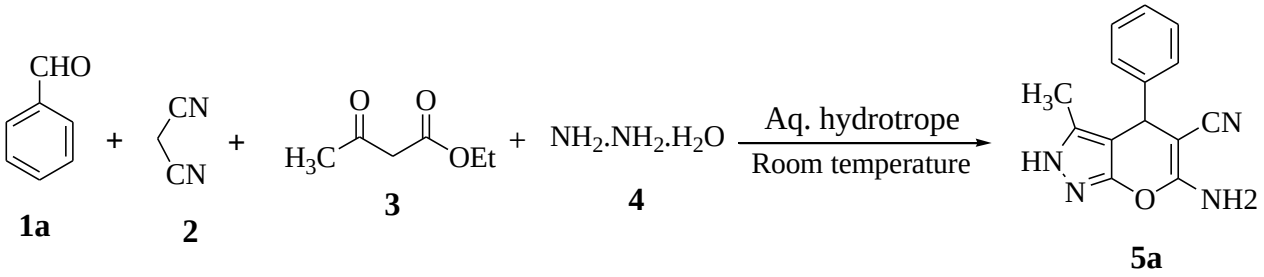
The fundamental challenge for today's researchers is the development of synthetic methodologies with environmental and economic benefits. The use of organic solvents in organic synthesis and industrial processes is often problematic because of their toxicity and flammability. Avoiding the use of organic solvents can reduce the generation of waste, which is one of the principles of green chemistry. One important feature of research towards green processes for organic synthesis is the scientific evaluation of potential replacements for volatile organic solvents. The solvents suitable for green chemistry are those that have low toxicity, are inert, degrade easily, and do not contaminate the product. Alternative reaction media to organic solvents include water [1]. Although the water is safe, benign, environmentally friendly and cheap compared with organic solvents but it is not much useful for most of the organic reactions as substrates are insoluble in aqueous medium and many reactive substrates, reagents and catalysts are decomposed or deactivated by water. In this context, the development of novel catalytic system which enables the use of water as a solvent for a wide range of organic transformations is strongly desirable. Aqueous solution of hydrotrope represents the unique properties of an alternative reaction media for organic synthesis. Moreover, being economic, non-toxic and environment friendly, aqueous hydrotropic solutions possess surplus physico-chemical characteristics required as alternative green solvents for organic reactions. Hydrotropes display important capacity to solubilize non-polar compounds in water [2] which leads to growing interest for the use of hydrotropes as solubilizing agents in organic processes [3-4]. Furthermore simple recovery from reaction mixture and recyclability makes hydrotropic medium as a green solvent for organic synthesis.

Pyrano[2,3-c]pyrazoles represent an interesting template for medicinal chemistry and play essential role as biologically active molecules [5]. Many of the pyrano[2,3-c]pyrazoles are known for their antimicrobial, insecticidal, anti-inflammatory and anticancer activities [6-7]. In addition, they are known to exhibit molluscicidal [8] and potent human Chk1 kinase inhibitor activities [9]. As a result, pyrano[2,3-c]pyrazoles have been imperative targets of numerous synthetic studies involving the use of catalysts such as glycine [10], L-proline [11], imidazole [12], per-6-amino-*β*-cyclodextrin [13], nanosized magnesium oxide [14], Cetyl trimethylammonium chloride [15], molecular sieves (MS 4A°) [16], Cocamidopropyl betaine as a biodegradable surfactant [17], ZrO_2 nanoparticles [18], etc. Multicomponent reactions (MCRs) play an important role in modern organic chemistry, because they generally

exhibit higher atom economy and selectivity as well as produce fewer by-products compared to classical multistep syntheses [19]. Furthermore, MCRs are easy to perform, inexpensive, quick, consuming less energy and involves simple experimental procedures [20]. Considering the importance of aq. hydrotropic solution in synthetic organic chemistry [21, 22] and in continuation of our research work to develop green chemistry methodologies [23-27], we aim to investigate the efficiency of aq. NaPTS hydrotropic solution for the synthesis of pyrano[2,3-c]-pyrazoles at room temperature.

Results and discussion

To optimize reaction conditions, we examined one-pot, four-component synthesis of 6-amino-4-phenyl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a**) by condensation of benzaldehyde (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol) and hydrazine hydrate (1 mmol) in aq. hydrotopic solution at room temperature (**Scheme** 1).



Scheme 1 Synthesis of pyrano[2,3-c]pyrazole using aq. hydrotropic solution

Initially the model reaction was run in water under stirring for 120 minutes at room temperature and observed trace amount of product (**5a**) formation. Then in order to increase the yield of product, the model reaction was screened for various hydrotropes such as sodium cumene sulphonate (NaCuS), sodium p-xylene sulphonate (NaXS) and sodium p-toluene sulphonate (NaPTS) and noticed that the concentration of hydrotropes has significant effect on the yield and time of reaction (**Table 1**). Among the various hydrotropes, aq. 50 % sodium p-toluene sulphonate (NaPTS) gave better yield (94 %) of desired product (**5a**) in 20 minutes at ambient temperature (Table 1, entry 5). In view of these observations we have selected aq. 50 % NaPTS as the reaction medium for the synthesis of pyrano[2,3-c]pyrazoles at room temperature.

Table 1 Screening and optimization of various hydrotropic concentrations for synthesis of pyrano[2,3-c]pyrazoles[a]

Entry	Conc. of catalyst (*w/v* %)	NaPTS		NaXS		NaCS	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	10	60	20	120	10	120	10
2	20	50	35	120	15	120	20
3	30	40	60	120	20	120	25
4	40	30	80	120	40	120	30
5	50	20	94	120	70	120	60
6	60	40	70	120	55	120	40
7	70	50	55	120	50	120	30

[a]Reaction condition: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), aq. hydrotropic solution (5.0 mL), at ambient temperature; [b]Isolated yields.

Next we have investigated the effect of reaction time on the yield of desired product (**5a**). **Figure 1** clearly indicates that the percentage yield of the product linearly increased with increase in reaction time from 5 to 20 minutes and increasing reaction time further to 35 minutes failed to increase the yield.

To explore the scope and generality of the developed protocol for the synthesis of pyrano[2,3-c]pyrazoles, variety of structurally diverse aldehydes were reacted with malononitrile, ethyl acetoacetate and hydrazine hydrate and results are summarized in **Table 2**. In all the reactions, the conversion was completed within 15-25 minutes with good to excellent yields of desired products. The nature of functional group on the aromatic ring of aldehyde exerted a slight influence on the reaction time. Studies revealed that aldehydes having electron withdrawing substituents reacted faster and gave better yield of the products as compared to the aldehydes with electron donating substituents.

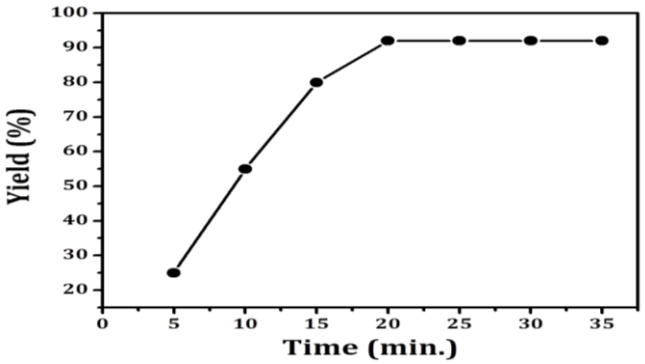
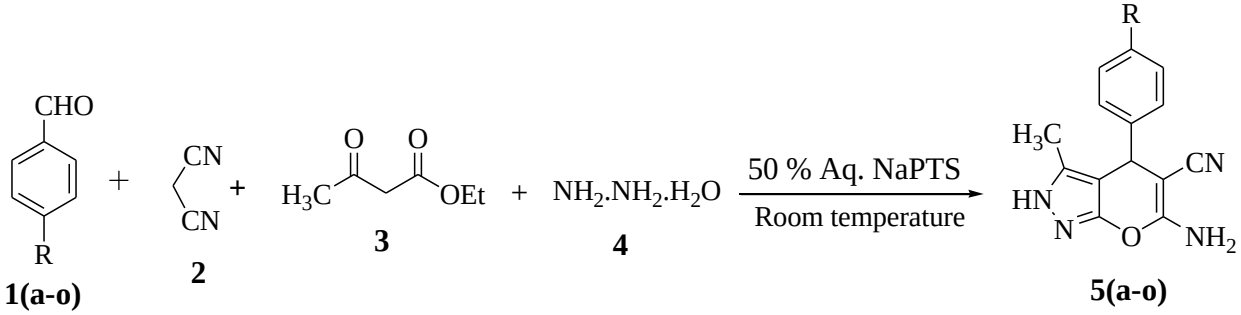
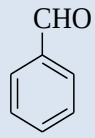
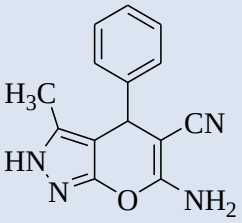
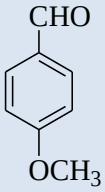
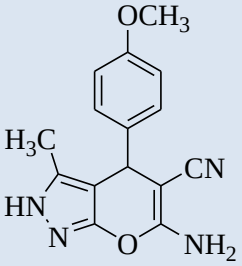
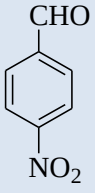
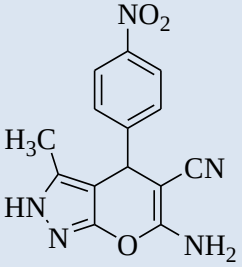


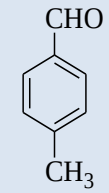
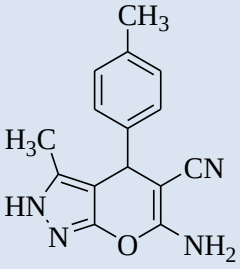
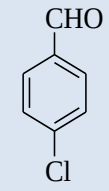
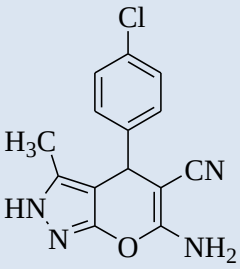
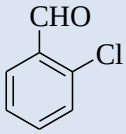
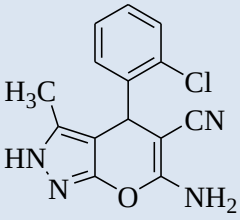
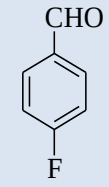
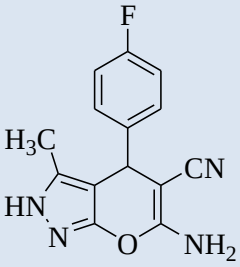
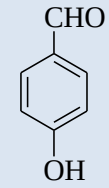
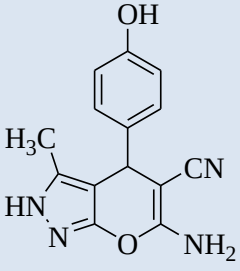
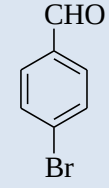
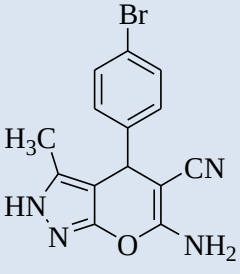
Figure 1 Optimization of effect of reaction time for the synthesis of pyrano[2,3-c]pyrazole

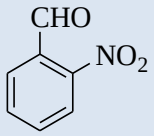
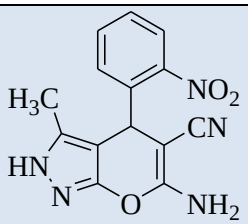
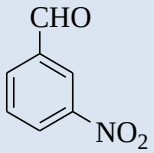
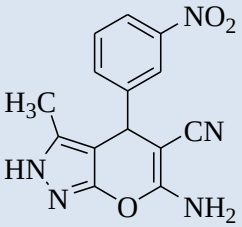
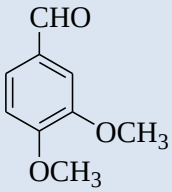
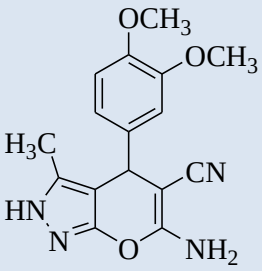
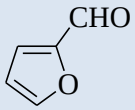
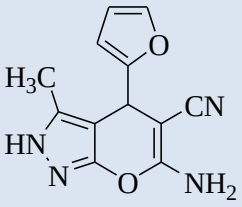
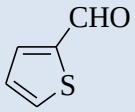
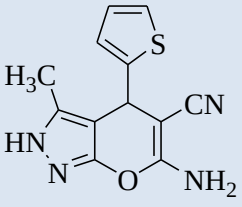
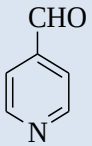
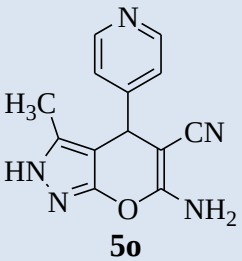
Table 2 Synthesis of pyrano[2,3-c]pyrazoles using 50 % aq. NaPTS solution[a]



1(a-o) **2** **3** **4** **5(a-o)**

Entry	Aldehyde	Product	Time (min)	Yield[b] (%)	M.P. °C [Lit.][Ref.]
1	 **1a**	 **5a**	15	94	168-170 [167-169][13]
2	 **1b**	 **5b**	20	87	208-210 [210-212][28]
3	 **1c**	 **5c**	20	91	188-190 [192-194][13]

4	 **1d**	 **5d**	25	88	172-174 [175-176][13]
5	 **1e**	 **5e**	15	90	174 [174-175][13]
6	 **1f**	 **5f**	20	89	240-244 [245-246][28]
7	 **1g**	 **5g**	15	92	172-174 [170-171][13]
8	 **1h**	 **5h**	20	90	220-222 [223-224][28]
9	 **1i**	 **5i**	20	92	174-176 [178-180][29]

10	 **1j**	 **5j**	20	88	218-220 [220-222][29]
11	 **1k**	 **5k**	20	89	185-189 [190-192][13]
12	 **1l**	 **5l**	20	86	190-194 [192-194][29]
13	 **1m**	 **5m**	25	89	170-172 [175-177][13]
14	 **1n**	 **5n**	25	89	192-194 [190-191][13]
15	 **1o**	 **5o**	25	90	216-218 [218-219][13]

[a]Reaction conditions: aldehyde (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and aq. NaPTS solution (5.0 mL) at ambient temperature.
[b]Isolated yield

A tentative reaction mechanism for the four-component synthesis of pyrano[2,3-c]pyrazole is shown in **Figure 2**. In the first step, the attack of hydrazine hydrate on ethyl acetoacetate results in to 3-methyl-1H-pyrazol-5-one (**A**) which undergoes tautomerization to form enol **B**. In the second step aldehyde reacts with malononitrile to generate

benzylidene malononitrile (**C**). Intermediates (**D**) and (**E**) generated from Knoevenagel-Michael addition reaction of (**B**) and (**C**) might have undergone intramolecular cyclization to yield pyrano[2,3-c]pyrazole derivative (**F**).

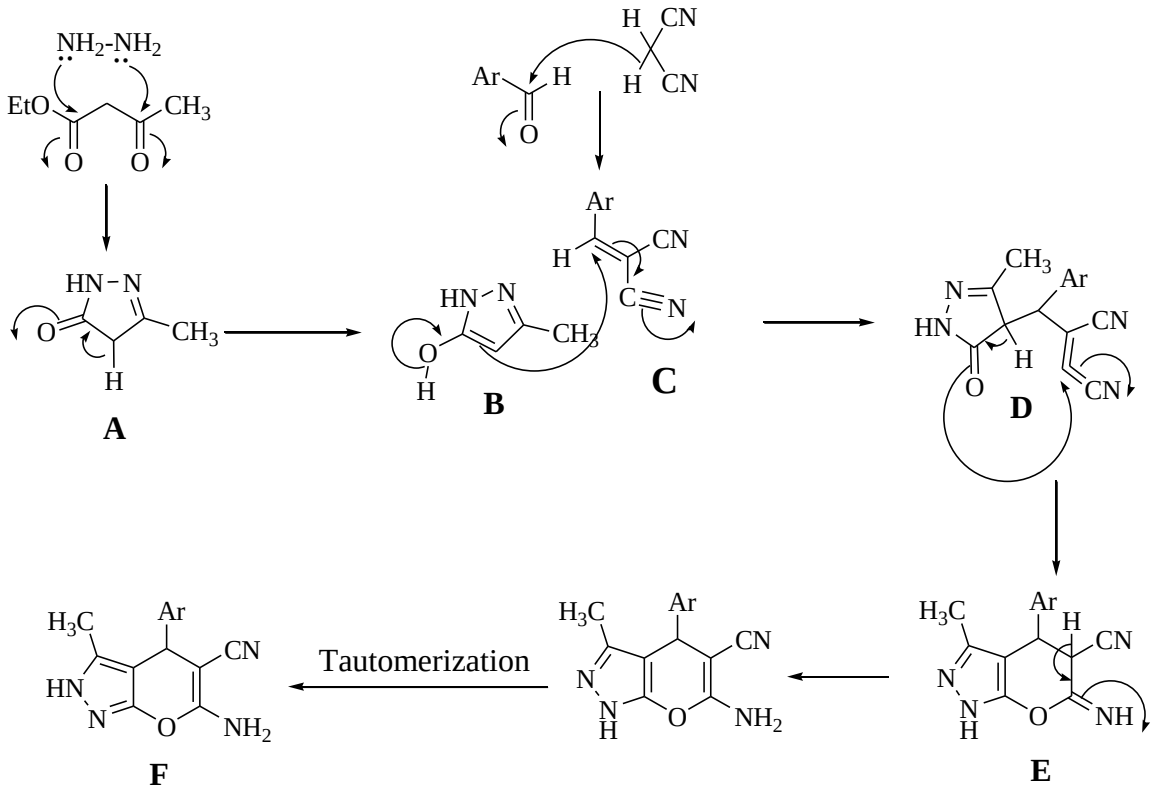


Figure 2 The plausible mechanism for the synthesis of pyrano[2,3-c]pyrazoles

To assess the reusability of aqueous NaPTS solution, recycling experiments were carried out with model reaction. After each experiment, reaction mixture was filtered and filtrate was washed with chloroform. The obtained aqueous phase was then subjected to a new run with fresh reactants and noticed that the aqueous NaPTS solution could be reused for at least four runs with a modest change in the yield of the product (**Figure 3**).

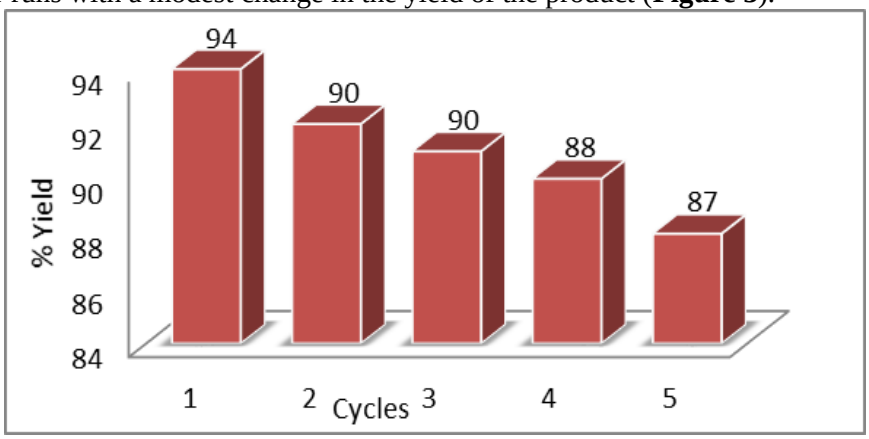


Figure 3 Recyclability of aq. NaPTS solution

Experimental section

General Remarks

All reagents and solvent were purchased from Merck and Sigma Aldrich and used without further purification. Melting points were determined in an open capillary and are uncorrected. Infrared spectra were obtained on Alpha-Bruker FT-IR spectrometer. The samples were examined as KBr discs ~5 % w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 300 MHz and 75 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal reference.

General procedure for the synthesis of 2,4-dihydropyrano[2,3-c]pyrazoles

A mixture of aldehyde (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol), and hydrazine hydrate (1 mmol) was stirred in aq. 50% NaPTS hydrotropic solution at room temperature for indicated time in Table 2. The reaction progress was monitored by TLC (petroleum ether/ethyl acetate, 8:2, v/v). After completion of the reaction the solid was filtered, washed with water and crystallized from ethanol to afford the pure 2,4-dihydropyrano[2,3-c]pyrazole derivatives. The synthesized products were confirmed by comparing the physical and spectral data (IR, ^{1}HNMR, ^{13}C NMR, MS) with those of the compounds reported in literature.

Conclusion

In conclusion, we have established an chromatography free methodology for the synthesis of pyrano[2,3-c]pyrazoles derivative utilizing aq. NaPTS hydrotropic solution as green reaction medium. In addition, the developed protocol has notable outcomes such as conversion under mild reaction conditions, tolerance of wide variety of functional groups and avoidance of organic volatile solvents.

Spectral data of representative compounds

6-Amino-3-methyl-4-(4-methylphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d)

White solid; mp. 201-204 °C. Vmax (KBr): 3471, 3324, 2198, 1656, 1592, 1386, 1065, 752 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.78 (s, 3H), 2.27 (s, 3H), 4.54 (s, 1H), 6.83 (s, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 12.07 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 10.2, 21.0, 36.3, 57.9, 98.2, 121.2, 127.8, 129.4, 136.0, 136.1, 141.9, 155.2, 161.2. MS (EI-MS): *m/z* 266 (M^+).

6-Amino-3-methyl-4-(4-chlorophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5e)

Yellow solid, mp. 230-234 °C; Vmax (KBr): 3369, 3258, 2190, 1644, 1564, 1387, 1122, 691 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.77 (s, 3H), 4.62 (s, 1H), 6.92 (s, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4, 2H), 12.18 (s, 1H), ^{13}CNMR (75 MHz, DMSO-d_6, δ ppm): 10.2, 36.0, 57.2, 97.6, 121.1, 128.9, 129.8, 131.6, 136.1, 143.9, 155.1, 161.3. MS (EI-MS): *m/z* 286.9 (M^+).

6-Amino-3-methyl-4-(4-bromophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5i)

White solid, mp.172-176°C; Vmax (KBr): 3387, 3135, 2183, 1601, 1486, 1396, 1041, 864 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.78 (s, 3H), 4.55 (s, 1H), 6.77 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.38-7.45 (m, 2H), 12.03 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 14.9, 41.0, 62.0, 102.1, 125.7, 132.0, 134.7, 136.4, 140.7, 148.8, 159.9, 166.0 ppm. MS (EI-MS): *m/z* 330 (M^+).

6-Amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5k)

Brown solid, mp. 185-189 °C; Vmax (KBr): 3474, 3223, 2195, 1654, 1597, 1408, 1077, 805 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.80 (s, 3H), 4.88 (s, 1H), 7.08 (s, 2H), 7.65 (d, *J* = 6.9 Hz, 2H), 8.03-8.14 (m, 2H,) 12.13 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 14.1, 36.1, 56.6, 97.1, 120.9, 130.7, 134.8, 136.3, 147.3, 148.3, 155.1, 161.6. MS (EI-MS): *m/z* 298 (M^+).

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